UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,007	02/01/2005	Neil Goldsmith	10-128	4661

20306 7590 11/23/2010

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
11/23/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,007	GOLDSMITH ET AL.	
	Examiner	Art Unit	
	CELINE X. QIAN	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7-9,11,15,16,18,23,26,28,30,36,39,43,44,49,54,57-60,62,80 and 102-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0710, 0710, 0910*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,2,4,5,7-9,11,15,16,18,23,26,28,30,36,39,43,44,49,54,57-60,62,80 and 102-104.

DETAILED ACTION

Claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 54, 57-60, 62, 80, 102-104 are pending in the application.

This Office Action is in response to the Amendment filed on 9/7/2010.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 54, 57, 59, 60, 62, 80, 102 and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delcardayre et al., in view of Peterson et al (US 5,783,431). This rejection has been re-written to address the amendment.

Delcardayre et al. disclose shuffling methods using artificial chromosome in yeast (see page 62, 3rd paragraph). Delcardayre et al. disclose construction of a YAC library, comprising DNA fragments obtained from a single organism or different individual or species (see bridging paragraph of 62-63). Delcardayre et al. also disclose that individual genes in the library can be linked to yeast regulatory elements to form an expression cassette, and a concatemer of expression cassettes, each containing a different gene, and such concatomers are inserted into YAC (see page 63, lines 5-9). Delcardayre et al. further disclose transforming the YAC library into yeast cells, wherein the cells are induced to under meiosis, and then induced to mate, following mating, the cells are screened/selected for a desired property (see page 63, 3rd

paragraph, and bridging paragraph of 63-64, and 2nd paragraph of page 64). Said process may be repeated until a desired property is acquired (see page 64, 3rd paragraph). Declardyare et al. disclose that each cell may harbor multiple YACs (page 65, line 14), and each YAC may contained two or more selectable marker (for example, a positive marker and a negative marker, see page 62, lines 24-25).

However, Delcardayre et al. do not teach an expression cassette comprising the general formula $[rs_2\text{-SP-PR-X-TR-SP-}rs_1]_n$, wherein rs_2 and rs_1 together denote a functional restriction site, SP individually denotes a spacer of at least two nucleotide bases, PR denotes a promoter, capable of functioning in a cell, X denotes an expressible nucleotide sequence, TR denotes a terminator, and n>=2, and wherein at least a first cassette is different from a second cassette, and substantially all cassette are recognized by the same restriction enzyme, and wherein the expression cassette also comprises and intron between the promoter and the expressible nucleotide sequence.

Peterson et al disclose a method of preparing vectors for expression libraries by linking multiple gene cassettes comprising (5'-3') a promoter, an expressible sequence, and a terminator, see Figs. 5A-5G and columns 47-67. Each cassette comprises, 5' to the promoter, SEQ ID NO: 5 (see column 9, lines 46-64) which comprises the nucleotide sequence 5' GATCTCT 3'. In this case, after *Bgl H* digestion, GATC is considered to be rs2 of the instantly claimed cassette and TCT the 5' spacer. Each cassette from Peterson et al also comprises, 3' to the terminator, SEQ ID NO: 11, which comprises the nucleotide sequence 3' CCCCTAG 5'. In this case, CTAG is considered to be rs1 of the claimed cassette and CCC the 3' spacer. In this instance, the rs2 and rs1 sequences, together, form the sequence GATC, which is a Mbo I restriction site. The

cassettes may differ in their expressible sequences, which may be derived from cDNA or genomic DNA from species as diverse as mammals and bacteria, e.g. as in claim 168 (column 8, lines 20 - 27, columns 17 -19, and Table I). The cassettes may be transformed into, for example, yeast cells (columns 57 - 59), and one such yeast strain may be *S. cerevisiae* (column 21, lines 36 - 37). The number of different library members (i.e. cassettes) may be up to 500,000 (¶ bridging columns 31 - 32) which may be used in concatentation reactions (columns 49 - 50). Peterson et al. also gave examples of making a concatemer expression cassette (see for example, section 5.4.6). Peterson et al. teach that a rare cutting enzyme Srf1 (a eight bp restriction enzyme) is used for concatenation of the cassette (see col.50, lines 1-38) in this example.

It would have been obvious to an ordinary skill in the art to make concatemers comprising the general formula $[rs_2\text{-SP-PR-X-TR-SP-}rs_1]_n$ as demonstrated by Peterson et al. and insert into the artificial chromosome to be mixed by mating the host cell and selecting a desired trait based on the teaching of Delcardayre et al. Delcardayre et al. teach the claimed method of mixing heterologous gene in expression cassette located on artificial chromosome, and indicates YACs comprising concatemers of expression cassettes that comprises different combination of genes and regulatory sequences may be used for this method. It would have been obvious to an ordinary artisan to construct the concatemer expression cassettes according to the teaching of Peterson et al. because the advantage of including different combination of genes and recovering said combination of genes is desired in the method taught by Delcardayre et al. It would also have been obvious to an ordinary artisan to varying the number of concatemers to at least 2 copies or 10 copies based on the need because it is contemplated by the teaching of Peterson et al. Using a rare restriction enzyme would have also been within the capability of an ordinary

skill in the art because such enzymes are readily available to the public by commercial vendor such as New England Biolab, wherein Peterson et al. also gives an example of using Srf1 during the process of concatemerization. Combining the prior art methods to achieve the predictable result is within the knowledge of an ordinary skill in the art. Therefore, the claimed invention would have been *prima facie* obvious to the ordinary artisan at the time the invention was made.

Response to Arguments

In response to this rejection, Applicants argue that neither Delcardayre nor Peterson alone or in combination teach or suggest the element of independent claim 1 that "rs1 and rs2 together comprise a rare restriction comprising a recognition sequence of 7 to 50 bases." Applicants argue that the disclosure of Peterson teaches away from the claimed invention because Peterson teaches using a rare cutting enzyme to release the concatemers from the solid support to reduce the probability of cleaving the concatenated DNA. Applicants allege that such teaching suggest Peterson intends to prevent subsequent cleavage between concatenated cassettes, which differs from the claimed invention wherein it uses rare restriction sites to facilitate subsequent cleavage between concatenated cassettes. Applicants thus conclude that the claimed invention is novel in view of the cited references.

The above argument has been fully considered but deemed unpersuasive. The details of the rejection have been set forth above. In response to the alleged deficiency, Applicants are reminded that Srf1 meet the limitation of rare cutting enzyme having a recognition sequence of 7-50 bases. Further, Applicants' characterization of Peterson's teaching at col.36, lines 13-17 is erroneous. The cited teaching only indicates that the cleaving of the concatenated DNA is undesirable when the concatenated DNA is released from the solid support, that is, during the

phase of making concatemers that comprising multiple transcription units, not in the subsequent steps as suggested by Applicants. In fact, in the example given by Peterson, it teaches the use of Srf1 for ligation between transcription units, a rare restriction enzyme. The existence of such recognition sites provides the possibility when subsequent cleavage is required. Therefore, the teaching of Peterson does not teach away from the claimed invention, but rather, render the claimed invention obvious (for reason discussed in the above rejection). This rejection is thus maintained.

Claim 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over Delcardayre et al., in view of Peterson et al (US 5,783,431) as applied to claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 54, 57, 59, 60, 62, 80, 102 and 104, in further view of Miao et al (US 7,351,813).

The teaching of Delcardayre et al. and Peterson et al. has been described above. However, none of the references teach inclusion of an intron between promoter and the expressible nucleotide sequence.

Miao et al. teach intron may be used in expression cassette. Miao et al. teach that short, functional, intron sequences are preferred in order to keep the size of the expression cassette as small as possible which facilitates the construction and manipulation of the expression cassette. Miao et al. teach the intron can be located at 5' to the coding sequence, 3' to the coding sequence, or within the coding sequence, wherein the advantage of locating the intron 5' to the coding sequence is to minimize the chance of intron interfering with the function of the polyadenylation signal (see col. 7, lines 41-58).

The obviousness of making concatemers comprising the general formula $[rs_2\text{-SP-PR-X-TR-SP-}rs_1]_n$ and insert into the artificial chromosome to be mixed by mating the host cell and selecting a desired trait based on the teaching of Delcardayre et al. and Peterson et al. has been discussed above. The inclusion of an intron in the expression cassette for the desired intronic effect such as splicing in a particular host is routine practice in the art as evidenced by Miao et al., and the teaching of Miao et al. further suggests the advantage of placing the intron 5' to the coding sequence, that is, in between promoter and the coding sequence. Combining the prior art methods to achieve the predictable result is within the knowledge of an ordinary skill in the art. Therefore, the claimed invention would have been *prima facie* obvious to the ordinary artisan at the time the invention was made.

Claim 103 is rejected under 35 U.S.C. 103(a) as being unpatentable over Delcardayre et al., in view of Peterson et al (US 5,783,431) as applied to claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 54, 57, 59, 60, 62, 80, 102 and 104, in further view of Smith et al. (PNAS, 1990. Vol.87. pages 8242-8246).

The teaching of Delcardayre et al. and Peterson et al. has been described above. However, none of the references teach inclusion of a conditional centromere in the artificial chromosomes.

Smith et al. teach inclusion of a conditional centromere that can be turned on or off by changing the carbon source in the yeast artificial chromosome (YAC), which allows copy number amplification of the YAC (see abstract).

The obviousness of making concatemers comprising the general formula $[rs_2\text{-SP-PR-X-TR-SP-}rs_1]_n$ and insert into the artificial chromosome to be mixed by mating the host cell and

selecting a desired trait based on the teaching of Delcardayre et al. and Peterson et al. has been discussed above. The inclusion of a conditional centromere on YAC is well known in the art for amplifying copy numbers of YAC in the host cell as evidenced by Smith et al. The ordinary artisan would thus recognize the advantage of such centromere and include such centromere on the YAC to of the claimed method for amplifying the copy number in the host cell, which will result in enhancement in screening process. Combining the prior art methods to achieve the predictable result is within the knowledge of an ordinary skill in the art. Therefore, the claimed invention would have been *prima facie* obvious to the ordinary artisan at the time the invention was made.

Response to Arguments

Applicants have not provided additional arguments for the above rejections but reiterated that the cited references fail to teach a rare restriction site. The argument is not considered persuasive for same reason as set forth above. The rejections are thus maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 52, 54, 56-60, 62, 80, 102-104 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method using yeast or fungal cells as host, does not reasonably provide enablement for the claimed method in other cell types such as mammalian, vertebrate, plant, insect cells. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention:

The claimed invention is drawn to a method of mixing heterologous genes in expression cassettes located on artificial chromosomes, comprising providing two initial population of cells that can mate with each other, each comprises at least two cells having different combinations of heterologous genes and/or expression cassettes, each cell comprises a first type of artificial chromosome comprising at least two expression cassettes comprising heterologous genes and selectable marker, selecting mated cells that carry at least a subset of the selectable markers presented in the two initial populations.

The breadth of the claim and the teaching of the specification:

The breadth of the claim with regard to the host cell, the initial cell population that comprises artificial chromosomes, in the context of the claimed method is broad. It encompasses any type of cell including eukaryotic cell such as mammalian, vertebrate, invertebrate animals,

plants, insect, and prokaryotic cells, etc. However, mixing heterologous expression cassettes located on artificial chromosome through the process of mating do not occur for mammalian, vertebrate, invertebrate, plant and insect cells. For prokaryotic cells such as bacteria, "mating," a process of equal exchange of genetic material or fusing of gametes and creation of a zygote, does not occur. Even if bacterial conjugation is considered "mating," it does not involve meiosis and mixing spores as contemplated by the claimed invention. The specification does not provide guidance for practicing the claimed method in host cells other than yeast or fungal cells. Therefore, the breadth of the claim exceeds the teaching of the specification.

The state of prior art and the predictability in the art:

The state of art at the time of filing does not provide teaching for how to accomplish the mating for the purpose of mixing heterologous gene cassettes located on the artificial chromosome and subsequent selection and meiosis in cells other than yeast and fungal species. In fact, the art teaches that the exchange of genetic material between cells such as mammalian, plant, insect, etc occurs through mechanism other than "mating." As such, whether the claimed method can be practiced with any type of cell is unpredictable. Without teaching from the specification and prior art, one skilled in the art would have to engage in undue experimentation to practice the claimed method to its full scope. Therefore, the claimed invention is only enabled to the scope as indicated above.

Response to Arguments

In response to this rejection, Applicants argue that independent claim 1 specifies that the cell should be able to mate or fuse with each other, thus the claims are not limited to those types of cells capable of mating. Applicants argue that cell fusion was well known in the art at the

time of filing. Applicants cited Ruthe and Adler for disclosing fusion of genetically different bacterial spheroplasts, resulting in strains of bacteria possessing a combination of genetic markers. Applicants further cited Karsten et al. to demonstrate that both electr4ic fields and polyethylene glycol can be used to fuse mammalian cells. Applicants also cited Constabel and Nakajima and Miyake to demonstrated PEG-induced fusion of plant cells and insect cells. Applicants thus conclude that the claimed invention is enabled to its full scope.

The above argument has been fully considered but deemed unpersuasive. The above teaching pointed out by Applicants merely states that bacterial cells, plant, insect cells and animal cell may fuse under certain condition. However, they do not teach whether host cell other than yeast and fungus is capable of carrying out the process as claimed. The claimed process not only requires the host cell to "fuse", it further requires the each host cell population having different combination of heterologous genes and/or different combination of expression cassettes, and each has at least first type of artificial chromosome that carries such expression cassettes, and shuffling cassette following the cell fusion. None of the cited references provide any teaching with regard to "fusing" in the context of the claimed method. As stated in the previous office action, other types of cell are not known to mate and having spores as claimed in claims 15, 16, 36, etc. As such, the specification does not provide object evidence that the claimed method can be carried out in cell other than yeast and fungus, with either mating or cell fusion process. Therefore, for reason set forth in the previous office action and above, this rejection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joanne Hama can be reached on 571-272-2911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian /
Primary Examiner, Art Unit 1636